HIV infection is associated with preservation of MAIT cells in the lungs but alteration of their phenotype and T cell receptor repertoire

Wong, E. B.; Xulu, B.; Prakadan, S.; Shalek, A. K.; Lalloo, U.; Baijnath, P.; Suleman, M.; Moodley, V.; Mitha, M.; Maharaj, P.

Total number of authors:
16

Published in:
Journal of the International AIDS Society

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

Tuesday 19 July

ORAL ABSTRACT SESSIONS

TUAA01 DRIVERS OF HIV PROGRESSION

TUAA0101

MICROBIAL TRANSLOCATION DURING HYPERACUTE SIV INFECTION

A. Ericsen[1,2], M. Lauck[3], M. Mohns[3], S. DiNapoli[4], J. Mutschler[5], J. Greene[3], J. Weinfurter[1], G. Lehrer-Brey[5], K. Crosno[5], E. Peterson[5], M. Reynolds[1], R. Wiseman[1], B. Burwitz[6,7], J. Sacha[6,7], T. Friedrich[5,8], J. Brenchley[4], D. O'Connor[1,5]
[1]University of Wisconsin-Madison, Pathology and Laboratory Medicine, Madison, United States, [2]University of Wisconsin-Madison, Virology Training Program, Madison, United States, [3]University of Wisconsin-Madison, Madison, United States, [4]National Institute of Allergy and Infectious Disease, Laboratory of Molecular Microbiology, Bethesda, United States, [5]Wisconsin National Primate Research Center, Madison, United States, [6]Oregon Health & Sciences University, Vaccine & Gene Therapy Institute, Beaverton, United States, [7]Oregon Health & Sciences University, National Primate Research Center, Beaverton, United States, [8]University of Wisconsin-Madison, Pathobiological Sciences, Madison, United States
Presenting author email: ericsen@wisc.edu

Background: Within the first weeks of human immunodeficiency virus (HIV) infection, virus replication reaches systemic circulation. Despite the critical, causal role of virus replication in determining transmissibility and kinetics of disease progression, there is limited understanding of the conditions required to transform a small localized transmitted founder population into a large and heterogeneous systemic infection.
Methods: Cynomolgus and rhesus macaques were infected with simian immunodeficiency virus (SIV) and followed longitudinally. Plasma levels of SIV were monitored using qRT-PCR. Bacterial genomic DNA in plasma was characterized and quantified longitudinally using 16S ribosomal deep sequencing and qPCR. ELISA-based assays were used to monitor intestinal permeability (IFABP) and perturbation of bacteria-specific host factors (sCD14 and EndoCab). Flow cytometry was used to track peripheral blood lymphocyte populations. In vitro assays were performed by exposing freshly-isolated peripheral blood mononuclear cells to bacterial lysate prepared from major translocators. Effects of bacterial lysate on CD4+ T cell activation and CD8+ T cell cytotoxicity was measured using flow cytometry. Statistical significance was calculated using ANOVA or Wilcoxon signed-rank testing.
Results: Prior to the peak of viremia, we observed a transient high-level influx of microbial genomic DNA into peripheral blood. This microbial translocation was accompanied by perturbation of bacteria-specific host factors in plasma, as well as expansion of the CD4+CCR5+ T cell compartment. Exposure of freshly-isolated peripheral blood mononuclear cells to lysate prepared from major translocating taxa revealed differential taxa-specific effects on the CD4+CCR5+ T cell compartment and cytotoxic granule expression within CD8+ T cells.
Conclusions: Altogether, our data identify the influx of microbial products into blood during hyperacute SIV infection as a candidate modifier of early interactions between the antiviral host response and nascent HIV infection. Over the next few months, we will explore the effect of inducing microbial translocation during SIV infection, with particular interest on microbial reactivity within the CD4+CCR5+ target cell compartment.

TUAA0102

IMPACT OF A FAT-RICH DIET ON THE PATHOGENESIS OF SIV INFECTION IN THE AFRICAN GREEN MONKEY HOST

C. Xu[1], T. He[1], G. Haret-Richter[1], D. Franck[2], B. Policicchio[1], E. Brocca-Cofano[1], D. Ma[1], J. Stock[1], R. Tracy[3], A. Landay[4], C. Wilson[2], C. Apetrei[1], I. Pandrea[1]
[1]University of Pittsburgh, Center for Vaccine Research, Pittsburgh, United States, [2]University of Colorado, Denver, United States, [3]University of Vermont, Burlington, United States, [4]Rush University, Chicago, United States
Presenting author email: cux1@pitt.edu

Background: High dietary fats were reported to induce intestinal dysbiosis, drive gut inflammation and breakdown the intestinal epithelial barrier, granting intestinal flora access to the bloodstream. As microbial translocation is a major determinant of the chronic immune activation and HIV/SIV disease progression, we investigated whether fat diet impacts HIV/SIV pathogenesis.
Methods: The nonprogressive African green monkey (AGM) model of SIV is an ideal system to assess the role of fat diet on disease progression, because they do not develop SIV-related intestinal dysfunction. We included 4 AGMs that received a fat diet prior and after SIVsab infection, and 5 controls in which the impact on key parameters of SIV infection such as: viral loads, CD4+ T cell counts, microbial translocation, immune activation and inflammation were compared and contrasted.
Results: LPS levels increased in the AGMs receiving fat diet prior and after SIV infection. Fat-rich diet also resulted in increases of immune activation (HLA-DR CD38, CD69 and Ki-67) and inflammation (inflammatory cytokines-IL-6, IL-17 and C reactive protein), leading to a prolonged depletion of CD4+ T cells compared to controls. However, these significant alterations of key parameters that are associated with the lack of disease progression in natural hosts of SIVs did not reach the levels described during progressive HIV/SIV infection. Furthermore, these changes did not result in significant increases in the levels of viral replication in the AGMs receiving a fat diet.
Conclusions: Administration of fat-rich diet resulted in alterations of markers of pathogenicity in the nonprogressive SIV infection of AGMs. Although not major, these changes were significant, suggesting that a diet very rich in fats may negatively impact HIV pathogenesis, especially if combined with other behavioral risk factors reported to impact gut integrity or systemic inflammation, such as alcohol consumption, drug usage and smoking. Detailed studies on the correlations between fat diet, alterations in the intestinal microbiota, metabolic markers, liver function and SIV progression to AIDS are in progress.

TUAA0103

HIV INFECTION IS ASSOCIATED WITH PRESERVATION OF MAIT CELLS IN THE LUNGS BUT ALTERATION OF THEIR PHENOTYPE AND T CELL RECEPTOR REPERTOIRE

E.B. Wong[1,2,3], B. Xulu[1], S. Prakadan[4], A.K. Shalek[4,5,6], U. Lalloo[7], P. Baijnath[8,9], M. Suleman[9], V. Moodley[9], M. Mitha[9], P. Maharaj[9], C. Costiniuk[10], M. Nielsen[11], Z. Mhlane[1], F. Karim[1], D. Lewinsohn[12], T. Ndung'u[1,5,13]
[1]KwaZulu Natal Research Institute for Tuberculosis and HIV, Durban, South Africa, [2]Massachusetts General Hospital, Division of Infectious Diseases, Boston, United States, [3]Harvard Medical School, Department of Medicine, Boston, United States, [4]Massachusetts Institute of Technology, Institute for Medical Engineering & Science and Department of Chemistry, Cambridge, United States, [5]Ragon Institute of Harvard, MGH and MIT, Cambridge, United States, [6]Broad Institute, Cambridge, United States, [7]Durban University of Technology, Durban, South Africa, [8]University of KwaZulu Natal, Department of Pulmonology and Critical Care, Durban, South Africa, [9]Inkosi Albert Luthuli Hospital, Department of Pulmonology and Critical Care, Durban, South Africa, [10]McGill University Health Center, Division of Infectious Diseases, Montreal, Canada, [11]Technical University of Denmark, Department of Systems Biology, Lyngby, Denmark, [12]Oregon Health and Sciences University, Division of Pulmonary Medicine and Critical Care, Portland, United States, [13]University of KwaZulu Natal, HIV Pathogenesis Programme, Durban, South Africa
Presenting author email: emily.wong@k-rith.org

Background: Tuberculosis remains the leading cause of death in HIV-positive people. A better understanding of the impact of HIV on lung immunity may lead to novel immunotherapeutic interventions. MAIT cells are tissue-homing donor-unrestricted T cells with broad anti-microbial activity. HIV infection causes early and irreversible depletion of MAIT cells in the peripheral circulation, but the effect of HIV on MAIT cells in the lungs is unknown.
Methods: We FACS-sorted MAIT cells from bronchoalveolar lavage (BAL) fluid and peripheral blood of HIV-infected and HIV-negative patients from Durban, South Africa. MR1-5OPRU tetramer staining was used to identify and phenotype MAIT cells based on expression of CD3, CD4, CD8, TRAV1-2, CD161 and CD26. High throughput bias-controlled TCR sequencing (ImmunoSEQ) of sorted populations enabled detailed analysis of TCRA CDR3a usage.
Results: HIV infection was associated with depletion of MAIT cells in the peripheral circulation (median %5OPRU+ of CD3+CD4- lymphocytes was 1.09% in HIV-negatives, 0.34% in HIV-positives, p = 0.027). In contrast, MAIT cells were not depleted in the BAL compartment during HIV infection (0.68% in HIV-negatives, 0.89% in HIV-positives, p = non-significant). In HIV-negative individuals, 77.1% of circulating MAIT cells expressed the expected CD161++CD26++ phenotype, but only 43.8% of BAL MAITs expressed this phenotype (p=< 0.0001). In HIV infected lungs, the frequency of MAITs with the CD161++CD26++ phenotype was significantly higher (57.6%) than in HIV-negative lungs (p=0.021). MAIT cells with canonical MAIT TCRA CDR3a rearrangements were highly shared between donors and clonally expanded in the BALs. MAIT cells with non-canonical TCRs were unique to individuals and more frequent in HIV-infection.
Conclusions: We report for the first time that MAIT cells in the lungs are numerically preserved but phenotypically and clonotypically altered by HIV infection. We confirm previous reports that circulating MAIT cells are depleted in HIV. Our results suggest that peripheral MAIT cell depletions observed in HIV infection may be due to compartment-specific microbial alterations and/or tissue redistribution. Further study is needed to determine the mechanisms underlying the altered phenotypes of lung-resident MAITs and whether these can be targeted to improve anti-microbial lung immunity in people living with HIV.